



CLINICAL CASE

Acute Hepatitis in the DRESS Syndrome



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KEYWORDS

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Sulfasalazine/adverse effects

Abstract Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, idiosyncratic reaction characterized by diffuse maculopapular rash, facial edema, lymphadenopathy, fever, eosinophilia and/or other leukocyte abnormalities, and involvement of internal organs as liver, kidney, heart and lung.

Diagnosing this entity is specifically complicated due to the multiplicity of organs involved. DRESS syndrome must be recognized promptly and the causative drug withdrawn in order to improve patient outcomes. Indeed, it is a potentially life-threatening condition, with a reported mortality between 5 and 20%.

We describe a case of a 22-year old woman admitted to our hospital with acute diffuse, pruritic rash associated with crampy abdominal pain, vomiting, diarrhea and fever three weeks after starting sulfasalazine therapy.

Initially, laboratory parameters revealed normal white blood cell count and normal liver enzymes, but during hospitalization, eosinophilia developed and liver enzymes, including transaminases and cholestatic parameters, dramatically increased. The diagnosis of DRESS syndrome was made and sulfasalazine was withdrawn and as there were signs of disease severity, systemic corticotherapy was initiated, with gradually improvement of the rash and symptoms resolution.

The patient was discharged home after thirty days of hospitalization.

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PALAVRAS-CHAVE

Doença Hepática Induzida por Medicamentos;
Falência Hepática Aguda/induzida quimicamente;

Hepatite Aguda na Síndrome DRESS

Resumo A síndrome DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) é uma reação de hipersensibilidade sistémica caracterizada por dermatite exfoliativa e rash maculopapular, linfadenopatia, febre, eosinofilia e envolvimento de órgãos internos, como o fígado e o trato gastrointestinal. O diagnóstico é difícil porque as suas manifestações clínicas mimetizam as encontradas noutras doenças sistémicas graves.

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Síndrome de
Hipersensibilidade a
Medicamentos;
Sulfassalazina/efeito
adverso

Esta síndrome deve ser reconhecida precocemente e o fármaco responsável suspenso com o intuito de melhorar o prognóstico do doente. É, de facto, uma condição potencialmente fatal, com uma mortalidade entre 5 e 20%.

Apresentamos o caso clínico de uma doente de 22 anos, que recorreu ao serviço de urgência por um quadro clínico caracterizado por rash pruriginoso associado a dor abdominal tipo cólica, vômitos, diarreia e febre 3 semanas após início de terapêutica com sulfassalazina.

Inicialmente, a avaliação laboratorial não revelou alterações, mas durante o internamento, desenvolveu-se eosinofilia e as provas hepáticas, incluindo transaminases e parâmetros de colestase, aumentaram de forma significativa.

Foi efetuado o diagnóstico de síndrome de DRESS, a sulfassalazina foi suspensa e iniciou corticoterapia sistêmica, dados os sinais de gravidade da doença.

Verificou-se melhoria gradual da sintomatologia, tendo tido alta clínica após trinta dias de internamento.

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1. Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a distinct, severe, idiosyncratic reaction to a drug characterized by a prolonged latency period.¹

The estimated incidence of this syndrome ranges from 1 in 1000 to 1 in 10,000 drug exposures.²

The main culprit drugs are carbamazepine and allopurinol, even though almost 50 drugs have been described to have caused this syndrome.²

The hallmark features of DRESS syndrome, not always detectable at the same time, include diffuse maculopapular rash, facial edema, lymphadenopathy, fever, hematologic abnormalities (eosinophilia or atypical lymphocytes),³ and involvement of internal organs.⁴

It is difficult to diagnose, as many of its clinical features mimic those found with other serious systemic disorders.⁵ However, early recognition of the syndrome with the cessation of the causative drug is essential in improving patient outcome.⁶

2. Clinical case

A 22-year old woman, born in Cape Verde, was being followed in the rheumatology outpatient setting for migratory oligoarthritis for seven years.

For this reason, sulfasalazine was started. After three weeks of treatment, she was admitted to our emergency department with an acute diffuse, pruritic rash. On admission, sulfasalazine was withdrawn and hydrocortisone was administered. Because she had no signs of end-organ damage or laboratory abnormalities, she was discharged home. After 3 days, she returned to our emergency department with the same clinical picture, now with crampy abdominal pain, vomiting, diarrhea and fever.

On admission, mental status was normal, body temperature was 36.3 °C, blood pressure was 140/84 mmHg, the heart rate was 76 beats per minute. She was alert and oriented and in no apparent distress.

Her skin had disseminated dermatosis with papules; there were also some pustules on the dorsal area, upper and lower limbs. There was no evidence of lymphadenopathy or hepatosplenomegaly.

Laboratory tests showed normal white blood cell count (6900 cell/ μ L) with absolute eosinophil count of 2300 cell/ μ L, with no atypical lymphocytes, liver parameters values: aspartate transaminase (AST) 58 IU/L; alanine transaminase (ALT) 68 IU/L; alkaline phosphatase (AP) 73 IU/L; gamma-glutamyl transferase (gGT) 50 IU/L; lactate dehydrogenase (LDH) 240 U/L; total bilirubin 0.25 mg/dL, with a normal prothrombin time (PT); serum creatinine level of 1.01 mg/dL; serum urea level of 35 mg/dL; C-reactive protein 6.64 mg/dL.

Dermatology was consulted and considered the skin lesions could be due to acute generalized exanthematous pustulosis induced by sulfasalazine (that had already been withdrawn) and a biopsy of one of the skin lesions was performed. Based on this diagnosis, prednisolone 20 mg/day and hydroxyzine 25 mg tid were initiated, with gradually improvement of the rash.

On the fourth day of hospitalization, she developed eosinophilia ($5.6 \times 10^3/\mu$ L), liver enzymes raised (AST 122 IU/L; ALT 207 IU/L; AP 184 IU/L; gGT 217 IU/L; LDH 718 U/L), maintaining fever and skin rash.

Due to sore throat on the sixth day after admission, Otolaryngology was consulted and observed tonsillitis with a grayish-white coating, recommending therapy with amoxicillin and clavulanic acid.

Liver enzymes continued increasing reaching maximum values on the eleventh day of hospitalization (AST 3591 IU/L; ALT 2102 IU/L; AP 573 IU/L; gGT 1591 IU/L; LDH 1940 U/L total bilirubin 2.11 mg/dL, also with elevation of PT (27, with normal value between 10 and 14). Abdominal ultrasound revealed only portal accentuation pattern. Due to the suspicion of toxic hepatitis, antibiotherapy was withdrawn.

Serologic tests for acute infection by hepatotropic virus – hepatitis A, B, C, E, Epstein–Barr virus, Citomegalovirus, human herpesvirus (HHV)-6 (evaluated by enzyme-linked immunosorbent assay) were negative.

Skin biopsy showed superficial perivascular lymphocytic infiltration.

The diagnosis of DRESS syndrome was made [using RegiSCAR criteria,⁷ the patient had 4 characteristics – acute skin rash, fever ($>38^{\circ}\text{C}$), involvement of liver, and eosinophils above the laboratory limits)]. For this reason, prednisolone was increased to 60 mg/day (1 mg/kg/day) with a progressive improvement in the rash. Similarly, liver enzymes which started reducing gradually, since one day after antibiotherapy withdrawal, returned to normal.

The patient was discharged home after thirty days of hospitalization (on 60 mg prednisolone/day), with the indication to gradually reduce corticosteroid therapy (slower reduction). After three months of follow-up, now on 40 mg prednisolone/day, the rash is in remission.

3. Discussion

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome formed by the acronym derived from the term "Drug Rash with Eosinophilia and Systemic Symptoms",⁶ was introduced by Bocquet *et al.*⁸ and was based on the observation of Callot *et al.*⁹ who, in 1996, performed a retrospective study of 24 patients: three patients had had subacute papulonodular or infiltrated plaques, without visceral involvement, while the remaining 21 patients had an acute widespread eruption, with fever, enlarged lymph nodes, and multivisceral involvement developed an acute systemic illness with eosinophilia.⁹

Although a dermatosis is common in DRESS, the extent of skin involvement is variable and therefore the 'R' in DRESS was subsequently changed from 'rash' to 'reaction'.⁶

The pathogenesis of DRESS syndrome is not well understood¹ but probably involves different mechanisms, including detoxification defects² leading to reactive metabolite formation and subsequent immunological reactions, slow acetylation, and reactivation¹ of human herpes,^{10,11} including Epstein-Barr virus, cytomegalovirus and HHV-6 and -7.^{2,12}

Many drugs have been reported to cause DRESS syndrome. Cacoub *et al.*, using the RegiSCAR scoring system, identified 44 drugs implicated in 172 cases reported between January 1997 and May 2009.² In this systematic review, the most common culprit drugs were aromatic anti-convulsants (carbamazepine, phenobarbital, phenytoin), allopurinol, lamotrigine, sulfasalazine, nevirapine, abacavir and mexiletine.²

This syndrome is usually characterized by long latency period between administration of the offending drug and symptom onset with a mean of 3.9 weeks (range 0.5–16 weeks).¹³ The delayed onset in relation to introduction of the causative drug is one of the important features of DRESS that can be distinguished from other types of drug eruptions.¹⁴

DRESS syndrome is a complex syndrome with a broad spectrum of clinical features.¹ The reaction often starts with fever shortly followed by rash, which is usually pruritic, and variable degrees of lymphadenopathy.¹⁴

The cutaneous eruption consists of a morbilliform rash.⁶ Initially, the upper trunk, face, upper extremities

are affected and followed by involvement of lower extremities.¹⁴

Swelling of the face, with marked periorbital involvement occurs in about 25% of patients.⁶ Tender lymphadenopathy can be seen in most patients (70–75%)⁶ early in the illness, affecting predominantly cervical nodes or generalized. Bilateral swelling of salivary glands with severe xerostomia is frequently observed.¹⁴

Other features of DRESS include visceral involvement (hepatitis, pneumonitis, myocarditis, pericarditis,⁶ nephritis, pancreatitis,¹¹ encephalitis,^{11,14} thyroiditis,¹⁴ colitis⁶).^{12,15} The liver is reported to be the most frequently involved internal organ.^{1,2,16}

There have been proposed three different diagnostic criteria.^{1,11} According to Bocquet *et al.* (in 1996), the diagnosis is established if there are at least three criteria present: skin eruption, hematologic abnormalities (eosinophilia $>1500/\text{mm}^3$; presence of atypical lymphocytes), and systemic involvement, including adenopathies ($>2\text{ cm}$ in diameter), hepatitis (transaminase elevation of at least twice the normal values), interstitial nephritis, interstitial pneumonia, or carditis.⁸ The Japanese study group of severe cutaneous adverse reactions to drugs (SCAR-J) criteria established other criteria (in 2006): maculopapular rash developing >3 weeks after starting with the suspected drug, prolonged clinical symptoms two weeks after discontinuing the causative drug, fever ($>38^{\circ}\text{C}$), elevation of liver enzyme (ALT $>100\text{ U/L}$), leukocytosis abnormalities [leukocytosis ($>11 \times 10^3/\mu\text{L}$), atypical lymphocytosis ($>5\%$) or eosinophilia ($>1.5 \times 10^3/\mu\text{L}$)], lymphadenopathy, and HHV-6 reactivation. Diagnosis of typical DRESS requires the presence of all 7 criteria.¹⁷ The European registry of severe cutaneous adverse reactions to drugs and collection of biological samples (RegiSCAR) group suggested the following criteria (in 2007) for hospitalized patients: reaction suspected to be drug related, acute skin rash, fever above 38°C , enlarged lymph nodes at at least two sites, involvement of at least one internal organ, blood count abnormalities: lymphocytes above or below the laboratory limits, eosinophils above the laboratory limits (in percentage or absolute count), or platelets below the laboratory limits. At least 3 of these criteria should be present for DRESS.⁷

According to RegiSCAR criteria, the patient described here met 4 characteristics: acute skin rash, fever, involvement of liver and eosinophilia.

The diagnosis, as shown in this clinical case, can be difficult because many of the clinical features can be nonspecific, and the syndrome often mimics infections (particularly bacteremia), neoplastic diseases (lymphoma, leukemia, hypereosinophilic syndrome, paraneoplastic), autoimmune or connective tissue conditions (adult-onset Still's disease, lupus erythematosus, vasculitis).^{6,10,11,15}

Although no definitive laboratory test exists for DRESS, a complete blood cell count can identify the characteristic leukocytosis with eosinophilia.¹⁸ Nevertheless, leukopenia and lymphopenia have been also reported and they occasionally precede leukocytosis.¹⁴

Hepatitis with isolated elevation of liver transaminases is common.⁶ A cholestatic injury pattern is seen in a minority of patients.¹⁹

Although the bilirubin may be normal at presentation, hyperbilirubinemia can develop even after the causative

drug is discontinued. Elevations in liver enzymes usually continue to persist for several days after discontinuation of the offending drug.¹⁴

Liver failure, although rare, contributes to the leading causes of death.⁶

The skin biopsy may help to confirm the diagnosis but is nonspecific.^{10,20} It shows a non-specific lymphocytic infiltrate of the papillary dermis, which may contain eosinophils and which is generally denser than in other drug reactions.²⁰

DRESS syndrome must be recognized promptly and the causative drug withdrawn.^{1,21,22} Indeed, it has been reported that the earlier the drug withdrawal, the better the prognosis.¹

However, clinical symptoms can be prolonged even after the withdrawal of culprit drugs. In fact, in the study performed by Kim *et al.*, which included 48 patients with DRESS syndrome, clinical manifestations persisted for 1 month.¹⁶ Empirical treatment with antibiotics or anti-inflammatory drugs should not be administered during the acute disease, since they may confuse or worsen the clinical picture of patients due to an unexplained cross-reactivity between drugs,¹⁴ as succeeded in our patient.

In 2010, the French Society of Dermatology published a consensus on the management of DRESS syndrome. According to this consensus, the absence of signs of severity, they recommend topical corticosteroids, emollients and H1-antihistamines. In the presence of signs of severity (transaminases greater than five times normal, renal impairment, pneumonia, haemophagocytosis or cardiac involvement), they propose corticosteroids equivalent to 1 mg/kg per day of prednisolone. If there are life-threatening signs: haemophagocytosis with bone marrow failure, encephalitis, severe hepatitis, renal failure, respiratory failure), they suggest steroids generally associated with intravenous immunoglobulin (IVIG) at a dose of 2 g/kg over 5 days. Finally, in the presence of signs of severity with confirmation of major viral reactivation, they recommend combining steroids and antiviral (ganciclovir) and/or IVIG.²¹

In this case, there were signs of severity as transaminases were greater than five times normal. For this reason, corticotherapy was initiated with a good response, albeit the difficulty in doing the diagnosis.

The mortality rate is reported to be between 5² and 20%^{6,22,23} and has been correlated with the degree of hepatic or renal involvement.¹⁴

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors have no conflicts of interest to declare.

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